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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/750,005	12/30/2003	Herbert T. Nagasawa	30451.2USU1	9934

26941 7590 10/19/2005

MANDEL & ADRIANO
55 SOUTH LAKE AVENUE
SUITE 710
PASADENA, CA 91101

EXAMINER	
HEARD, THOMAS SWEENEY	
ART UNIT	**PAPER NUMBER**
1654	

DATE MAILED: 10/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/750,005	NAGASAWA ET AL.	
	Examiner	Art Unit	
	Thomas S. Heard	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7,9,10,20-22,25,26,33-35,38,39,46,47,50 and 51* is/are pending in the application.

4a) Of the above claim(s) *5-6, 8, 11-19, 23-24, 27-32, 36-37, 40-45, 48-49, and 52-104* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7,9,10,20-22,25,26,33-35,38,39,46,47,50 and 51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 12/30/03 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date March 07, 2005; July 21 2004
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I and the elected species L-CySSG in the reply filed on 09/01/2005 is acknowledged. The traversal is on the ground(s) that there is not a serious search burden imposed in the examiner in searching both the methods and the compositions. Applicants further traverse that do not require restriction under 808.01(a). This is not found persuasive because the search for elected species L-CySSG would not reveal CySSMA as they are distinct and independent species, with a different core structure and are patently different, see 808.01(a). There is a serious burden on the examiner in searching all of the inventions because they are not co-extensive particularly with regard to the literature search. Further, a reference that would anticipate the invention of one group would not necessarily anticipate or even make obvious another group. Finally, the consideration for patentability is different in each case. The applicants are not even sure that a search of the prior art would reveal the sulfhydryl protected glutathione prodrugs as the Applicant stated "should" reveal rather than would reveal. Thus, it would be an undue burden to examine all of the above inventions in one application and the restriction for examination purposes as indicated above is deemed proper.

The requirement is still deemed proper and is therefore made FINAL.

The applicant has canceled claims 5-6, 8, 11-19, 23-24, 27-32, 36-37, 40-45, 48-49, and 52-104. Claims 1-4, 7, 9, 10, 20-22, 25-26, 33-35, 38, 39, 46, 47, 50, and 51, are to be examined on the merits.

The references that were included in the form 1449 have been considered but those listed elsewhere in the response have not been considered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 7, 9, 10, 20-22, 25-26, 33-35, 38, 39, 46, 47, 50, and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Demopoulos et al, US Patent 6,159,500 and Eriksson, Stellan A. and Bengt Mannervik, The Reduction of the L-cysteine-Glutathione Mixed Disulfide in Rat Liver, FEBS Letters, March 1970, 742):26-8.

The instantly claimed invention is drawn to a method of treating a number of diseases through reducing oxidative stress in the cell by raising glutathione levels with a glutathione prodrug, L-CySSG designated as CySSG or CSSG throughout the office action.

Demopoulos et al teaches a method of treating oxidative stress through the administration of GSH (glutathione). Demopoulos et al defines oxidative stress as "low intracellular levels of reduced GSH, see column 4 and lines 39 and 40. Demopoulos et al also teaches that "a number of disease states have been specifically associated with the reduction in glutathione levels" and that "clinical and pre-clinical studies have demonstrated the linkage between a range of free radical disorders and insufficient GSH levels, see column 3 and lines 22-45. Demopoulos et al teaches that 'glutathione status is a major determinant of protection against oxidative injury." Demopoulos et al teaches that "glutathione may also hold benefit for the treatment of parotitis, cervical dysplasia, Alzheimer's disease, Parkinson's disease, aminoquinoline toxicity, gentamycin toxicity, puromycin toxicity, aminoglycoside nephrotoxicity, paracetamol, acetaminophen and phenacetin toxicity." Demopoulos et al teaches that "Glutathione exists in plasma in four forms: reduced glutathione (GSH), oxidized glutathione (GSSG), mixed disulfide with cysteine (CySSG) and protein bound through a sulfhydryl linkage (GSSPr). The distribution of glutathione equivalents is significantly different than that of cyst(e)ine, and when either GSH or cysteine is added at physiological concentration, a rapid redistribution occurs. The distribution of glutathione equivalents in rat plasma is 70.0% protein bound, with the remaining 30% apportioned as follows: 28.0% GSH, 9.5% GSSG, and 62.6% as the mixed disulfide [CySSG] with cysteine." Further, Demopoulos et al teaches that "The ubiquitous tripeptide L-glutathione (GSH) (gamma-glutamyl-cysteinyl-glycine), is a well known biological antioxidant, and in fact is believed to be the primary intracellular antioxidant for higher organisms. When oxidized, it forms

a dimer (GSSG), which may be recycled in organs having glutathione reductase. Glutathione may be transported through membranes by the sodium-dependent glutamate pump." Demopoulos et al does not teach that CySSG is in equilibrium with GSSG.

Eriksson, Stellan A. and Bengt Mannervik, The Reduction of the L-cysteine-Glutathione Mixed Disulfide in Rat Liver, FEBS Letters, March 1970, 742):26-8, teaches that CySSG is in equilibrium with GSSG, thus demonstrating that al components are capable of being replenished through the addition of any of the four forms taught by Demopoulos et al, see the results section where CySSG + GSH = CySH + GSSG is figured.

It would have been obvious at the time of the invention to use the compounds of glutathione, (GSH), oxidized glutathione (GSSG), mixed disulfide with cysteine (CySSG), to replenish the intracellular concentration of such an important small molecule. Given the rapid distribution of GHS in the plasma and the bodies (cells) ability to recycle GSSG and CySSG, any one of the four forms of glutathione would be capable of raising the intracellular concentration of the needed glutathione. It would be obvious to use any glutathione precursor that is capable of raising the glutathione levels in any disease. One would be motivated to do given Demopoulos et al teaching of the benefits and importance of glutathione in the management of oxidative states of the cell and it's role in disease states. Therefore, the invention as a whole is prima facia obvious over the prior art.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thomas S. Heard whose telephone number is (571) 272-2064. The examiner can normally be reached on 9:00 a.m. to 6:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

TSH

Bruce Campell

BRUCE R. CAMPELL, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600